CHARACTERIZING MEDICATION ADHERENCE TO AN ORAL GLUCOSE LOWERING DRUG, METFORMIN USING GROUP BASED TRAJECTORY MODELS

by

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Abstract

Background

Medication non-adherence is a major contributor to suboptimal control of chronic diseases. Its consequences include inferior clinical outcomes as well as unnecessary health care costs. Group based trajectory models (GBTM), a type of finite mixture model, can be used to identify distinct trajectories of medication adherence among the patient population. It models adherence as a longitudinal parameter.

Objective

To characterize patterns of medication adherence among adult patients in the first year of initiating metformin using group based trajectory models, compared to the traditional summary measure of proportion of days covered.

Methods

We identified patients who initiated metformin, an oral glucose lowering drug, between 1st January to 31st December, 2011 from pharmacy prescription claims in Truven MarketScan Commercial Claims and Encounter database and followed them for a period of 360 days. We evaluated the number of days covered by metformin in 12 30 day periods and generated 12 monthly indicators to indicate whether that month was fully covered (defined as 24 or more days out of the 30 days). We modeled trajectories using group based trajectory models (2 to 6 groups) using these monthly indicators. We also calculated a traditional summary measure, proportion of days covered (PDC). We used Bayesian Information Criterion (BIC), posterior probabilities and clinical relevant interpretations in order to decide the best fit model. Additionally, we compared the accuracy of prediction of adherence of the different summary measures.

Results

Among 77,279 patients who initiated metformin in 2011, we found that the 5 and 6 group model performed comparably. Overall the 6 group trajectory model summarized long term adherence best (C statistic 0.951) and PDC categorized as 80% or more (value of 1) and less than 80% (value of 0) summarized adherence worst (C statistic 0.767). However, keeping in the mind the relevance of clinical interpretation, we chose the 5 group model to be best fit model.

Conclusion

Group based trajectory models can be used to summarize medication adherence more accurately than proportion of days covered. This newer method can be used by payers, clinicians and researchers in order to identify groups of patients with distinct adherence patterns and to identify targeted interventions for its improvement.

Preface and Acknowledgement

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I. Introduction

Healthcare costs in the United States have been increasing at an alarming rate over the last few decades. Not surprisingly, a large portion of the spending is allocated towards patients with chronic diseases. A recent publication by the Non-communicable Disease Risk Factor Collaboration estimated the direct annual economic burden of diabetes mellitus globally in 2014 to be $825 billion, with the United States ($105 billion) coming second only to China ($170 billion).[1] Similarly, the total direct and indirect cost of cardiovascular disease and stroke in the United States in 2010 was calculated to be $315.4 billion.[2] Optimal disease management and control of these patients not only requires good medical care on the side of the healthcare providers but also effective implementation of self-management on part of the patients.

Medication non-adherence is a major contributor to poor control of chronic diseases. The consequences of non-adherence include inferior clinical outcomes as well as unnecessary health care costs. A paper evaluating the economic benefit of medication adherence showed that for every additional dollar spent on adhering to a prescribed medication, medical costs would be reduced by $7.10 for diabetes, $5.10 for hypercholesterolemia, and $4 for hypertension.[3] A systematic review by Bitton et al[4] observed that high adherence to statins for secondary prevention of coronary artery disease reduced annual hospitalization costs by 10%-17%. Non-adherence to medications among patients with type 2 diabetes mellitus is associated with worse control of intermediate risk factors, higher odds of hospitalization and healthcare costs and increased risk of mortality.[5 6]

Medication adherence depends on a complex interplay between patients' characteristics, their behavior and environment, the healthcare system and the disease.[7] Traditionally, the norm in adherence research has been to classify patients as 'adherent' and 'non-adherent' based on a threshold, often taken as 80% days covered by the medication.[8] It is increasingly being recognized that these broad classes are an oversimplification and there is potential to improve upon them. There is a large body of ongoing research aimed at designing interventions to improving adherence, ranging from empowering the patients themselves with mHealth initiatives[9] to involving pharmacists and other healthcare workers to be part of the solution.[10-12] However, when it comes to actual implementation, it has been clear for a while that the one size does not fit all. In order to individualize the interventions, we must go beyond categorizing patients as adherent and non-adherent. Two individuals who have been adherent to a drug 50% of the time could have different longitudinal patterns; one might be adherent only for the first few months of a treatment while the other could be intermittently adherent throughout the treatment course. Understanding and identification of these patterns can give us clues for customizing interventions that can have the maximum impact.

Group based trajectory models, as conceptualized by Nagin et al[13 14] and used extensively in social and behavioral research, identify distinct trajectory patterns of any exposure within the data without external specification of the structure of the groups. This method had recently been used by Franklin et al to model medication adherence to statins as a longitudinal parameter.[15] The rationale was that there might be meaningful subgroups in the population that follow distinct adherence trajectories which are not identifiable ex ante on the basis of some measured characteristics such as age, gender,

education, etc. and that there are actual distinctive adherence patterns in the population; always adherent vs. adherent for the first few months vs adherent intermittently vs. never adherent.

Diabetes mellitus is common chronic metabolic disorder which affects a large portion of the population globally. A recent statistic observed that the prevalence of type 2 diabetes mellitus and pre-diabetes in the overall population of the United States in 2011-2012 was 14.3% (95% CI 12.2% -16.8%) and 38% (95% CI 34.7% - 41.3%) respectively.[16] Despite the availability of many drug classes and frequently updated international and national guidelines, a substantial proportion of the population fails to achieve their glycemic goals. While several factors may contribute to this, lack of adherence to the recommended treatment is considered an important factor. Several studies have shown that medication adherence to oral glucose lowering drug ranges from 65-85% while adherence to insulin ranges from 60-80%[17] and that poor adherence is associated with worse glycemic control.[18]

I propose to characterize adherence to metformin, a first line oral treatment for type 2 diabetes, using group based trajectory models as compared to the traditional measurement, proportion of days covered, in patients who have newly initiated this drug.

II. Objectives

Specific aim 1. To characterize patterns of medication adherence among adult patients in the first year of initiating metformin using group based trajectory models.

Hypothesis: There are several distinct trajectories of medication adherence in the population, which can be modeled as a longitudinal process using group based trajectory models.

Specific aim 2. To compare group based trajectory models and the proportion of days covered as summary measures of medication adherence

Hypothesis: Group based trajectory models will summarize adherence better than a traditional measurement, proportion of days covered.

Specific aim 3. To identify the factors associated with the distinct trajectories, including patient demographics, healthcare utilization, comorbidities, and polypharmacy.

Hypothesis: Younger age, higher burden of prescription drugs and presence of certain comorbidities are associated with lower adherence.

III. Methods

Data source

We used the 2010-2012 Truven MarketScan Commercial Claims and Encounters database. The MarketScan database contains data from over 75 million patients including active employees, early retirees, Consolidated Omnibus Budget Reconciliated Act (COBRA) continues and dependents insured by employer-sponsored plans in the United States. The dataset captures individual level information about their demographic characteristics, clinical services utilization, expenditures, enrollment across inpatient, outpatient and prescription drug services. We used national drug codes (NDCs) from RED BOOK™ available from Truven Health Analytics to identify the prescription drugs in the pharmacy claims data.

Cohort derivation

The study population included all patients who newly initiated metformin monotherapy in the year 2011 and had one year complete follow up information (Figure 1). We chose metformin as our drug of interest as it is well established as the first line drug recommended by the American Diabetes Association.[19] We identified patients who filled their first prescription for metformin from a retail pharmacy between 1st January and 31st December, 2011 from the outpatient pharmacy claims data. Index date was defined as the date of the first prescription claim. To make sure that the included patients were incident users, we only included those who had continuous enrollment in the database in the 12 months preceding the index date with no prescription of any glucose lowering medications (oral or injectable) during that time.

We excluded patients filling index prescriptions by mail since their adherence may differ from those using retail pharmacies.[20] We required that complete information about age, sex, fill date, day supply and source of pharmacy fill (whether retail or mail pharmacy) be available. In order to plot the trajectories of medication adherence for one year, we included patients who had 12 months continuous enrollment after the index date (regardless of subsequent prescription refill). We excluded patients switching drug classes or starting dual therapy during follow up.

Adherence measures

We summarized adherence to metformin using two methods - the proportion of days covered (PDC) and the group based trajectory models (GBTM). To calculate these measures, we followed patients for the next 360 days (12 'months' of 30 days each) after the index date and extracted all dates of prescription fill along with the number of days' supply dispensed. If the pharmacy fill for the drug on any given day was more than 180 days, we truncated the fill at 180 days.

We created a separate dataset where an array of binary indicators was generated, one for each day of the follow up. It was coded as 1 if that day was covered by metformin and 0 otherwise, using the above extracted information. If the subsequent fill occurred before the end of days' supply for the previous fill, we assumed that the newly dispensed drug was used after the prior fill was exhausted. We then created a summary 'monthly indicator' for each 30 day period (1 – 30 days, 31 to 60 days and so forth) with 0 indicating less than 80% coverage translating to 23 days or less coverage of drugs for that month and 1 indicating 80% or more coverage translating into 24 days or more coverage for the month. We chose the cut off of 80% for categorizing adherence as it has been

widely accepted as the threshold for optimal adherence in research. It is also the coverage which is recommended by the WHO to be reached for achieving potential benefits of diabetes medications.[8] These binary 'monthly indicators' for 12 months were the variables of interest which were modelled in the group based trajectory model. Additionally, we calculated the traditional summary measure of adherence i.e. the proportions of days covered (PDC) for the entire 360 day period as well as dichotomized PDC into 80% or more being fully adherent and less than 80% being non-adherent.

Group based trajectory model

We used group based trajectory model (GBTM), a type of latent class analysis model, to classify patients according to their medication adherence trajectory. The advantage of the group based trajectory models over conventional growth models is that instead of assuming everyone follows a similar adherence trajectory with a population mean adherence trajectory, it assumes that there are clusters of distinctive trajectories of medication adherence that reflect unique etiologies or behaviors. Not everyone's adherence patterns will increase over time; some might stay the same, some might decrease and GBTM allows for this freedom. Standard growth curve models aim to identify the factors which account for individual variability about the population's mean adherence trajectory while the GBTM frames inferences based on the trajectory groups i.e. what factors distinguish group membership. An important assumption of the model is of conditional independence.[21] It states that repeated measures on the same individual are independent within the same trajectory and the within person correlation structure is explained completely by their trajectory.

We explored the data and fit 5 separate trajectory models, with the number of groups ranging from 2 to 6. We limited the maximum number of trajectory groups to 6 as we felt it would be difficult to interpret the clinical significance and usefulness of too many trajectories. To allow the trajectories to be flexible and not be constrained by symmetry, we added the square and cubic terms of time to the trajectory. Here the trajectory is allowed more than one peak or trough and can turn multiple times. The output of a group-based trajectory model includes estimated probabilities of group membership for each individual, proportion of entire population in each group and an estimated trajectory curve over time for each group. We used a Stata version 13[22] plugin, with the command *traj,* for estimating group based trajectory model as developed by Jones and Nagin.[23] Maximum likelihood is used for the estimation of the model parameters.

Model diagnostics

Nagin et al has suggested the use of average posterior probability (APP) of assignment as a diagnostic tool to evaluate the accuracy of the group membership probabilities. The posterior probability is the probability that an individual with a specific adherence pattern belongs to a specific trajectory group.[21] The output of the model creates a separate variable for each group which contains the probability of being in that group for every individual in the population. For example, consider that we are modelling a 4 group trajectory model and we have posterior probabilities generated for a patient as 0.2 for group 1, 0.6 for group 2, 0.3 for group 3 and 0.9 for group 4. Here, the patient has the highest probability of being in group 4 (0.9 vs 0.2, 0.3 and 0.6) and hence, the patient will be assigned to group 4. Ideally the APP should as close to 1 as possible. An average

posterior probability of 0.7 is considered as a minimum threshold for all groups. We calculated the mean/standard deviation as well as median/inter quartile range of the posterior probabilities of each group. The Bayesian Information Criterion (BIC) was also used to select the model with the best fit as recommended in the trajectory literature,[13] with higher score indicating better fit. Ultimately, the model selection was done using both the above mentioned criteria as well as clinical interpretation and usefulness of the generated trajectories.

Comparing adherence summaries

We compared different measurement methods i.e. the total PDC over follow up, dichotomized PDC and GBTM having 2 to 6 distinct groups to see which method best summarized the observed medication adherence. We assigned a separate adherence summary for every patient and person month (total 12 months in the follow up). In case of total PDC and dichotomized PDC, the summary measure was the same across person months but varied for each patient. In case of the group based trajectory models, the adherence summary measures were different across the person-months but were the same for all members of the same group. We combined the summary measures for all person-months that were fully covered (monthly indicators were 1) and those that were not covered by metformin (monthly indicators were 0) and calculated the mean, median and the interquartile range. The summary measures for the months that were fully covered needed to approximate 1 and the months that were not fully covered needed to approximate 0. We used C-statistics to see how well the estimated summary measures ("test values") compared to the observed ("the gold standard" measure of binary

indicators indicating more than 80% adherence during the month). A C-statistic of 1.0 indicates perfect association while a value of 0.5 indicates no association.

Covariates

We examined the distribution of certain covariates in the study population as well as across the trajectory groups determined by the best fit model. The demographic covariates included age, sex, region in the US and patient's health plan. As polypharmacy has been shown to influence adherence, we calculated the number of unique drugs filled in the 6 months before index date of prescription. Hertz[24] et al and Kirkman[25] et al observed that the presence of cardiovascular diseases such as hypertension and hyperlipidemia, either identified by ICD-9 codes or by their prescription drug fill, were associated with higher adherence to glucose lowering drugs and depression was associated with reduced adherence. Additionally, we noted the details of the initial metformin therapy – amount of copay, whether a brand or generic was initiated, which formulation – immediate or extended release was initiated. These data are composed of de-identified patient information, hence it was considered exempt research by the Institutional Review Board of Johns Hopkins University.

IV. Results

A total of 77,297 patients who initiated metformin monotherapy in 2011 were included in the study. The distribution of baseline characteristics of the included patients is given in Table 1. The majority of the patients belonged to the age group of 45 to 54 years of age (32%), were males (59%) and lived in the southern region of United States (46%). The average number of unique prescriptions filled out in the last 6 months was 6 (±3.9) with a wide range of 1 to 50. A substantial proportion of patients had filled a prescription for cholesterol lowering drugs (35%) and anti-hypertensives (beta blockers 16%, ACE inhibitors/ARBs 35%). One in five patients had filled a prescription for an antidepressant in the 6 months prior to index date. Keeping in line with the prescription fills, almost one third of the patients had a physician's visit with a diagnosis of hypertension, hyperlipidemia and depression in the 6 months before index prescription.

G*roup based trajectory models*

Figure 2 shows the various distinct trajectories identified by the group based trajectory models (with groups ranging from 2 to 6). We can see that the probability of adherence varies across time for all patients, which is captured within the trajectories. Table 1 details the distribution of patients across the different groups for all models. For example, in the 2 group model, the patients are categorized into two groups, one with high probability of adherence, which includes 41.8% patients and one with rapidly declining probability of adherence, including 58.2% of patients. As the number of groups are increased (2 through 6), we observe that the extreme groups (almost fully adherent and non-adherent after index prescription) persist and many patients are redistributed in

the middle groups where distinct adherence patterns emerge. With the 6 group model, we observed that 16.3% of the patients were almost always adherent, Group 1; 14.9% of the patients were found to be intermittently adherent through of the year, Group 2; adherence of 12.8% of the patients declined in the first few months but then increased slightly (occasionally adherent) over the next 6 months, Group 3; 11.9% of the patients had slowly declining adherence after the index prescription was filled, Group 4; 21.3% of the patients had slow declining adherence, Group 5; and 22.8% were non-adherent after the first fill, Group 6 (Figure 2, Panel E).

We assessed the model with the best fit using BIC values and the average posterior probabilities of being in each group. These details are given in Table 2 and 3. We observed that the BIC values was the largest for the GBTM specifying 6 groups. For each of the group based trajectory models (with 2 group, 3 group, 4 group etc.), we calculated the average posterior probability of being in each group. The APP was higher than the threshold of 0.7 across all groups and all models. We saw that the patients assigned to the consistently extreme groups (consistently adherent vs. non-adherent after index prescription) had the highest APP values, nearing 1, while the patients assigned to other groups had lower APP values in models specifying 3 to 6 groups.

Comparing adherence summaries

We compared the different methods of summarizing adherence as given in table 2. We calculated the average summary measures for each method separately, for months which were categorized as non-adherent (less than 23 days coverage of the 30 day period) and the months which were categorized as adherent (24 or more days coverage of the 30 day period). There were 496,805 person-months in the one year follow up period which

was not fully covered by metformin. In these months, better performing adherence summaries would have low values, close to 0 – showing that the summarized adherence was similar to the observed adherence from the data. There were 430,759 person-months in the one year follow up period which was fully covered by metformin. In these months, better performing adherence summaries would have values close to 1 (estimated closer to the observed). For example, for person-months fully covered by metformin where the observed or 'true' probability of being adherent is 1, group based trajectory models with 2 groups estimated that the average probability of being adherent was 0.73±0.23 compared to PDC overall which estimated that the average probability of being adherent was 0.77±0.25. Similarly, for person-months not covered by metformin where the observed or 'true' probability of being adherent is 0, group based trajectory models with 2 groups estimated that the average probability of being adherent was 0.23±0.26 compared to PDC overall which estimated that the average probability of being adherent was 0.36±0.22.

Among the conventional methods of summarizing adherence, we observed that overall PDC approximated 1 (0.77±0.25) in fully covered person-months but performed poorly in non-covered person months and the PDC categorized into adherent and non-adherent (0 or 1) performed very well for non-adherent months (0.06 ± 0.24) but fared poorly in fully covered person-months (0.59±0.49). Group based trajectory models, even the 2 group model, summarized adherence better for both covered and non-covered person months compared to conventional methods and further improvement was seen as the number of groups increased from 2 to 6. The C-statistic, which compared the 'test' values to the 'gold' standard, improved as the number of groups specified were increased

in group based trajectory models. Overall the 6 group trajectory model summarized long term adherence best (C=0.951) and binary PDC summarized adherence worst (C=0.767).

The performance of the 5 group and 6 group models were comparable. However, the selection of the best fit model was not only based on statistical parameters but also its appropriate clinical interpretation. We decided that the distinct trajectories generated by 5 group model captured the underlying medication adherence behaviors which could potentially be applied to identifying appropriate interventions and be clinically meaningful. In the 5 group model, we observed that around one fourth of the patients (24.8%) were almost always adherent, 12.9% of the patients were intermittently adherent through of the year, 12% of the patients had slowly declining adherence after the index prescription was filled, 24.7% of the patients had rapidly declining adherence and 22.9% were non-adherent after the first fill.

Characteristics across the 5 groups

When we assessed the distribution of the baseline characteristics for the 5 groups, we observed that the group which was poorly adherent to metformin (group 5) had a larger proportion of patients in the age group of 18 to 34 years, were more likely to be male and did not have any prescription filled for more than 60 days (Table 4). The number of unique prescription filled in the last 6 months were similar across the 5 groups. The group containing patients who were almost always adherent (Group 1) had a higher proportion of prescription fills for cholesterol lowering drugs, anti-hypertensives such as beta blockers, ACE inhibitors and angiotensin receptor blockers, which falls as the groups become less adherent (Group 2 to 5). When we observe the comorbidities identified, we see a similar pattern. The patients in Group 1 are more likely to have

hypertension and hyperlipidemia versus group 5. The proportion of patients in Group 1 (almost always adherent) who had an outpatient visit for depression in the 6 months before index prescription was lower than in Group 5 (poorly adherent). The proportion of patients on antidepressants were comparable across the groups.

V. Discussion

The present study determined that the group based trajectory models summarize adherence more accurately than the conventional adherence summary measure, proportion of days covered. Our results demonstrate that there are distinct patterns of medication adherence to metformin in the population which can be further examined and understood. Among the number of groups evaluated, the 5 group model was selected as the best fit model on the basis of clinical interpretation and statistical considerations.

As suggested by Nagin et al, we used many criteria to select the model with the best fit including BIC and average posterior probabilities.[21] We saw that the average posterior probabilities were almost perfect (near 1) with the 2 group model and continued to be high (more than 0.9) as the number of groups specified increased. This demonstrates that the probability of being in the assigned group was high among patients indicating that group assignment was largely accurate. Due to the large sample size of the study, it was expected that the model fit would improve even if we empirically tested more groups (7 and more). However, the clinical meaning of a large number of groups would be ambiguous. Hence we limited the number of groups to 6.

Conventionally, methods to measure adherence are classified as subjective or objective.[26] [27] The studies which utilize pharmacy or administrative claims data use pharmacy fill dates reported as part of the claims process to calculate adherence. Since group based trajectory models were first evaluated by Franklin et al in 2013 to summarize medication adherence to statins,[15] other researchers have used this method for assessing adherence to anti-glaucoma medications in a managed care population,[28] heart failure medications using pharmacy claims[29] and biologics for psoriasis.[30]

The area of adherence research has been flooded with interventions aimed at its improvement. Interventions can be classified as educational, either one-on-one or group sessions; behavioral such as packaging and dose modifications, and mail or telephone reminders; affective such as counselling sessions, home visits etc;[31] economic or multifaceted, involving multiple interventions.[32] A recent systematic review done by Saptoka and colleagues showed that majority of the interventions aimed at type 2 diabetes mellitus patients were educational and behavioral in nature.[32] However, only a small number of interventions were effective, which were largely multifaceted in their approach. The trend towards precision medicine can also be applied to medication adherence with a move towards individualizing interventions based on the observed adherence patterns.

We noted that modeling adherence using group based trajectory models may help identify broad classes of patients as well as certain interventions which may selectively benefit certain populations. These interventions can be empirically tested for their effectiveness. In our results, we observed that around a fourth of the patients were highly adherent. While these patients were more likely to have prescriptions for other chronic diseases, they may not require any interventions except regular interactions and follow up with healthcare professionals. The patients who are intermittently adherent after the first few months might benefit from a combination of reminder messages from the pharmacy as well as sessions of diabetes self-management education while patients who are almost always non-adherent may favor affective interventions such as one on one counselling sessions as well as home visits. We can also use GBTM identify patient and disease factors associated with specific trajectories. If patients who are almost always non-

adherent are found to have many comorbidities and active prescriptions, they might benefit by specialized pharmacy services such as compliance or calendar packaging.[33] For example, a study evaluating an outpatient pharmacy clinical service (OPCS) program targeting non-adherent diabetes mellitus and coronary artery disease patients showed significant improvement in medication persistence levels.[34]

Some foundational work has been done in exploring how the new adherence summary measure can be used in research as well as in clinical practice. Franklin et al have shown that the adherence summarized by GBTM is a better predictor of future adherence than the traditional methods or even high dimensional propensity scores.[35 36] Furthermore, these models have been evaluated for their ability to predict future clinical outcomes. A study done among statin users and future cardiovascular events observed that better predictive performance with trajectory models compared to proportion of days covered.[37]

Curkendall et al[38] studied the predictors of medication adherence among patients with type 2 diabetes mellitus and found that around 45% of total patients were adherent (defined as more than 80% coverage) over one year of follow up. Adherence was found to be higher among males, older age, living in non-Southern states, with mail order use and lower levels of cost sharing. Hertz et al[24] found that around 37% of patients discontinued pharmacotherapy within 12 months of initiation. Our findings that group with high levels of adherence had larger proportion of patients with hypertension and hyperlipidemia and fewer patients on antidepressants corroborated results observed by Hertz et al.[24]

There were a few limitations of the study. Proportion of days covered is a measure of drug coverage with an assumption that coverage is a proxy for adherence. However, we cannot be certain that the patient is actually taking the medications as per the physicians' instructions. Additionally, there were a large proportion of index prescriptions filled for 60 to 90 days. In these cases, the patients are credited with being in possession for more days because of the bigger dispensing. As we are taking the first prescription fill as our starting point, the patients who were actually prescribed metformin by the physician but failed to fill it were missed. In fact, they might the patients who need the most effective interventions. We also only analyzed patients who were prescribed metformin alone, which is a subset of all diabetic patients. Nevertheless, the aim of the study was primarily to evaluate the performance of group based trajectory model rather than draw causal associations and conclusions.

Diabetes mellitus has been a prominent non-communicable disease for many decades. Evidence suggests that the epidemic may have plateaued with fewer new incident cases being diagnosed[16] but it still leaves us with a large population with high economic and healthcare burden. New drugs are constantly being designed with an intent to satisfy unmet needs in the population but optimal utilization of currently available drugs is vital. The place of group based trajectory models in the field of adherence research need to be investigated further. We intend to extend this study further into looking at the association of different adherence patterns with clinical outcomes as well as understand how patterns of medication adherence may change with time dependent factors. Given the promising preliminary research, this method can be used in order to empirically test effectiveness of interventions, aid clinicians and payers in identifying

patients who are poorly adherent to medications earlier and ultimately reduce healthcare costs by improving clinical outcomes.

VI. References

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VII. Tables

Table 1. Characteristics of the overall study population (n=77297)

Characteristics	Percentage
Age, %	
18 to 34 years	15.9
35 to 44 years	20.3
45 to 54 years	31.8
55 to 64 years	32.0
Male sex, %	59.3
Region, %	
Northeast	10.1
North Central	22.7
West	46.1
South	16.3
Unknown	4.8
Index prescription – copay amount, %	
$0	25.9
$0.1 to $9.99	58.7
$10 to $19.99	13.1
More than $20	2.3
Index prescription – Brand/Generic, %	
Brand	1.1
Generic	98.9
Index prescription – day supply, %	
Less than 15 days	1.4
16 to 30 days	86.8
31 to 60 days	2.5
61 to 90 days	8.8
91 to 180 days	0.4
Formulation of metformin, %	
Immediate release	92.8
Extended release	7.2
Average number of unique drugs filled in the last 6 months	6 ± 3.9
Mean ±SD (Range)	(1 – 50)
Prescriptions filled in last 6 months, %	
Cholesterol lowering drugs	35.0
Beta – blockers	16.0
ACE Inhibitors/ARBs	35.0
Antidepressants	20.0
Comorbidities, %	
Hypertension	38.2
Depression	3.0
Hyperlipidemia	36.9

SD – Standard deviation, ACE – Angiotensin converting enzyme, ARB – Angiotensin receptor blocker

Table 2. Distribution of patients across groups in various Group Based Trajectory Models

GBTM model	Groups	Percentage of patients	Posterior probability of being in the group	
			Mean (±SD)	Median (IQR)
2 group model	Group 1	41.9	0.98 (± 0.07)	1.0 (1.0 – 1.0)
	Group 2	58.1	0.98 (± 0.07)	1.0 (1.0 – 1.0)
3 group model	Group 1	28.1	0.96 (± 0.09)	1.00 (0.98 – 1.00)
	Group 2	30.8	0.92 (± 0.12)	0.98 (0.85 – 0.99)
	Group 3	41.1	0.95 (± 0.10)	0.99 (0.96 – 1.00)
4 group model	Group 1	27.9	0.95 (± 0.10)	0.99 (0.97 – 1.00)
	Group 2	16.7	0.86 (± 0.16)	0.95 (0.75 – 0.99)
	Group 3	16.2	0.87 (± 0.15)	0.96 (0.81 – 0.98)
	Group 4	39.2	0.92 (± 0.15)	0.99 (0.92 – 1.00)
5 group model	Group 1	24.8	0.96 (± 0.1)	0.99 (0.98 – 1.00)
	Group 2	12.9	0.85 (± 0.17)	0.94 (0.74 – 0.99)
	Group 3	12.0	0.84 (± 0.16)	0.92 (0.71 – 0.98)
	Group 4	27.4	0.93 (± 0.13)	0.99 (0.93 – 1.00)
	Group 5	22.9	0.9 (± 0.03)	0.9 (0.9 – 0.9)
6 group model	Group 1	16.3	0.89 (± 0.08)	0.92 (0.92 – 0.92)
	Group 2	14.9	0.92 (± 0.14)	0.99 (0.91 – 1.00)
	Group 3	12.8	0.9 (± 0.14)	0.97 (0.84 – 0.99)
	Group 4	11.9	0.84 (± 0.15)	0.88 (0.71 – 0.98)
	Group 5	21.3	0.9 (± 0.1)	0.94 (0.91 – 0.97)
	Group 6	22.8	0.92 (± 0.01)	0.92 (0.92 – 0.92)

GBTM – Group based trajectory model, IQR – interquartile range, SD – Standard deviation

Table 3. Table comparing the summary values of different trajectory models with 2 to 6 groups with traditional measures

Model	Fully adherent months (N = 430,759)		Non-adherent months (N = 496,805)		C statistic	BIC
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)		
PDC	0.77 (0.25)	0.86 (0.61 - 0.98)	0.36 (0.22)	0.30 (0.14 - 0.53)	0.876	-
PDC – binary	0.59 (0.49)	1.00 (0.00 - 1.00)	0.06 (0.24)	0.00 (0.00 - 1.00)	0.767	-
GBTM - 2 groups	0.73 (0.23)	0.81 (0.77 - 0.85)	0.23 (0.26)	0.10 (0.09 - 0.26)	0.891	-421350.40
GBTM - 3 groups	0.77 (0.24)	0.90 (0.65 - 0.92)	0.20 (0.25)	0.03 (0.02 - 0.39)	0.925	-396895.14
GBTM - 4 groups	0.78 (0.23)	0.92 (0.61 - 0.93)	0.18 (0.25)	0.03 (0.02 - 0.34)	0.935	-388537.95
GBTM - 5 groups	0.80 (0.23)	0.92 (0.68 - 0.94)	0.16 (0.24)	0.05 (0.00 - 0.22)	0.946	-381773.23
GBTM - 6 groups	0.81 (0.23)	0.88 (0.72 - 1.00)	0.16 (0.25)	0.00 (0.00 - 0.24)	0.951	-379752.27

PDC – Proportion of days covered; GBTM – Group based trajectory models; SD – standard deviation; IQR – Interquartile range; BIC – Bayesian Information Criterion

Table 4. Characteristics of the study population according to the 5 group trajectory model

Characteristics	Group 1 (n=19148)	Group 2 (n=10010)	Group 3 (n=9311)	Group 4 (n=21150)	Group 5 (n=17678)
Age, %					
18 to 34 years	6.2	10.6	13.5	21.2	24.2
35 to 44 years	13.7	19.1	19.5	23.4	24.7
45 to 54 years	35.4	35.6	33.5	29.7	27.5
55 to 64 years	44.8	34.7	33.4	25.7	23.7
Male sex, %	50.1	55.3	57.6	63.3	67.8
Region, %					
Northeast	12.1	9.8	11.0	9.3	8.6
North Central	24.5	22.0	23.3	21.6	22.3
West	40.5	46.7	45.7	48.5	49.2
South	17.1	16.0	15.4	16.1	16.3
Unknown	5.9	5.6	4.7	4.5	3.6
Index prescription – copay amount, %					
$0	27.2	25.7	25.5	25.6	25.1
$0.1 to $9.99	58.1	58.7	57.8	57.9	60.9
$10 to $19.99	12.9	13.3	13.9	13.6	12.1
More than $20	1.8	2.4	2.8	2.9	1.9
Index prescription – Brand/Generic, %					
Brand	0.7	1.0	1.3	1.2	1.3
Generic	99.3	99.0	98.7	98.8	98.7
Index prescription – day supply, %					
Less than 15 days	0.9	1.3	1.0	1.1	2.7
16 to 30 days	83.3	86.4	80.5	85.4	96.0
31 to 60 days	2.7	2.1	2.9	3.2	1.3
61 to 90 days	12.4	10.0	14.6	9.9	0.0
91 to 180 days	0.6	0.2	1.1	0.4	0.0
Number of unique drugs filled in the last 6 months Mean ± SD (Range)	6.43±4 (1-47)	6.1±3.9 (1- 34)	6.1±3.9 (1-37)	5.8±3.9 (1 – 41)	5.7±3.9 (1 – 50)

Characteristics	Group 1 (n=19148)	Group 2 (n=10010)	Group 3 (n=9311)	Group 4 (n=21150)	Group 5 (n=17678)
Prescriptions filled in last 6 months, %					
Cholesterol lowering drugs	48.1	40.4	37.6	28.7	24
Beta – blockers	21.9	17.5	17.3	12.7	11.7
ACE Inhibitors/ARBs	44.8	40	37.7	30.6	25.6
Antidepressants	20.8	21.1	21.1	19.2	18.7
Comorbidities, %					
Hypertension	45.7	43.3	40.1	34.3	30.6
Depression	2.6	2.8	3.1	3.1	3.2
Hyperlipidemia	44.8	41.7	39.3	32.9	29.3

SD – Standard deviation, ACE – Angiotensin converting enzyme, ARB – Angiotensin receptor blocker

VIII. Figures

Figure 1. Derivation of study cohort

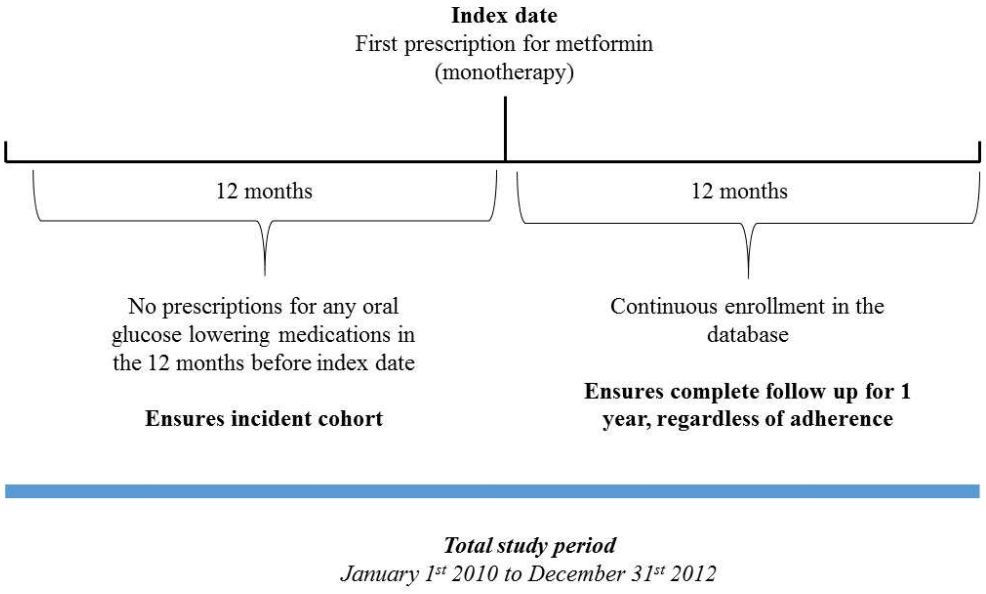
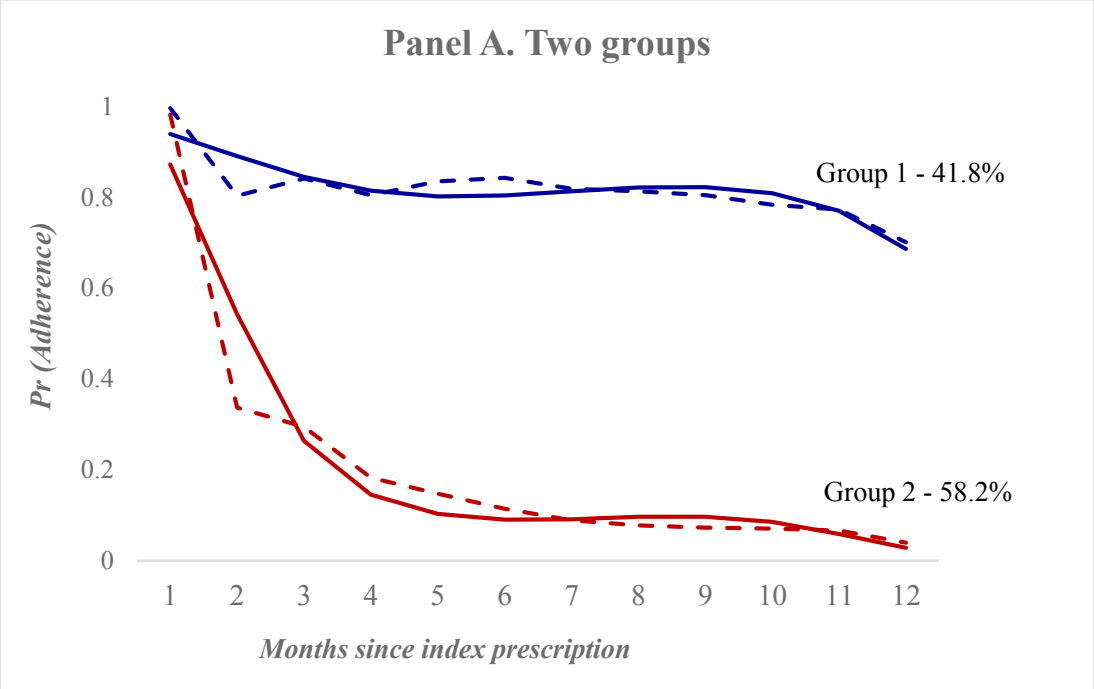
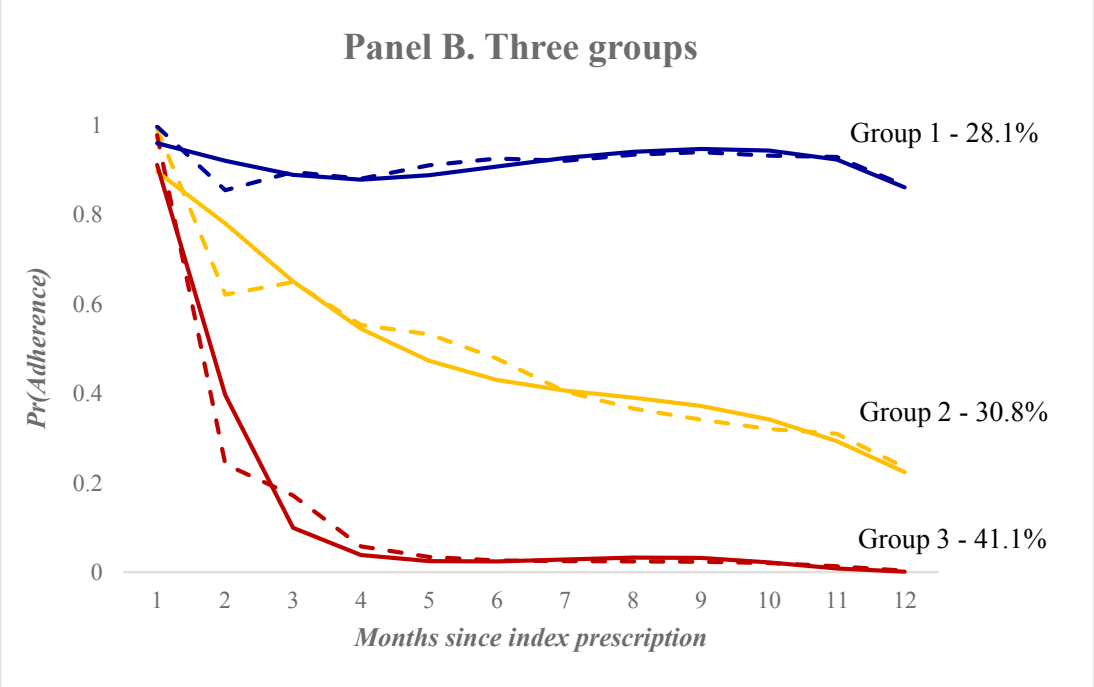
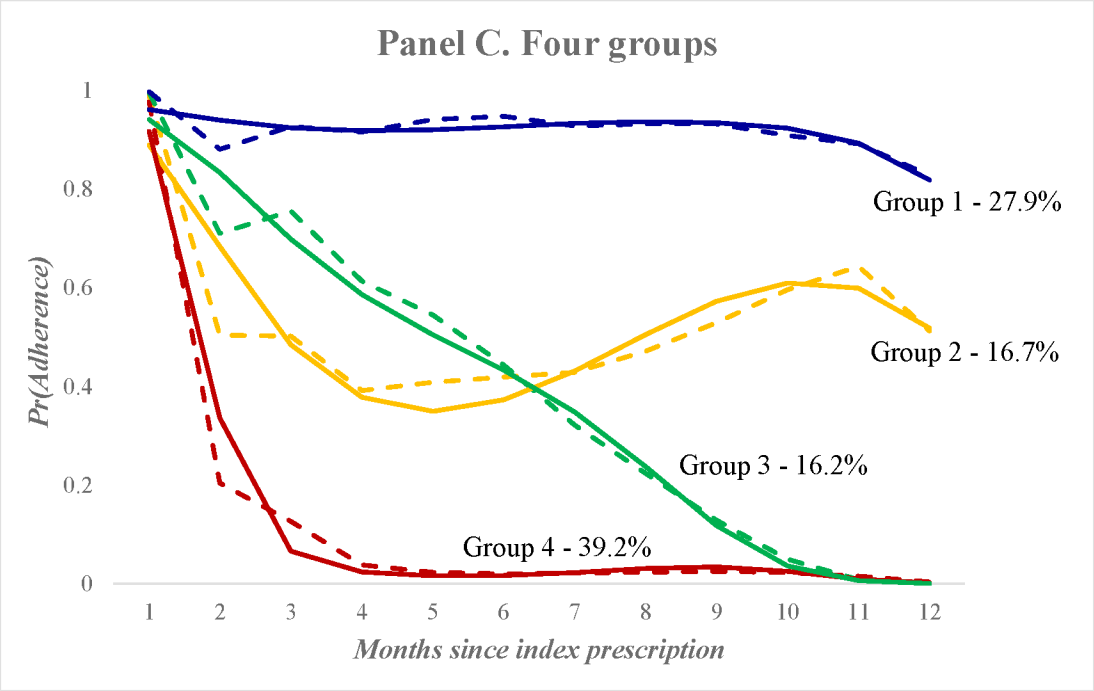
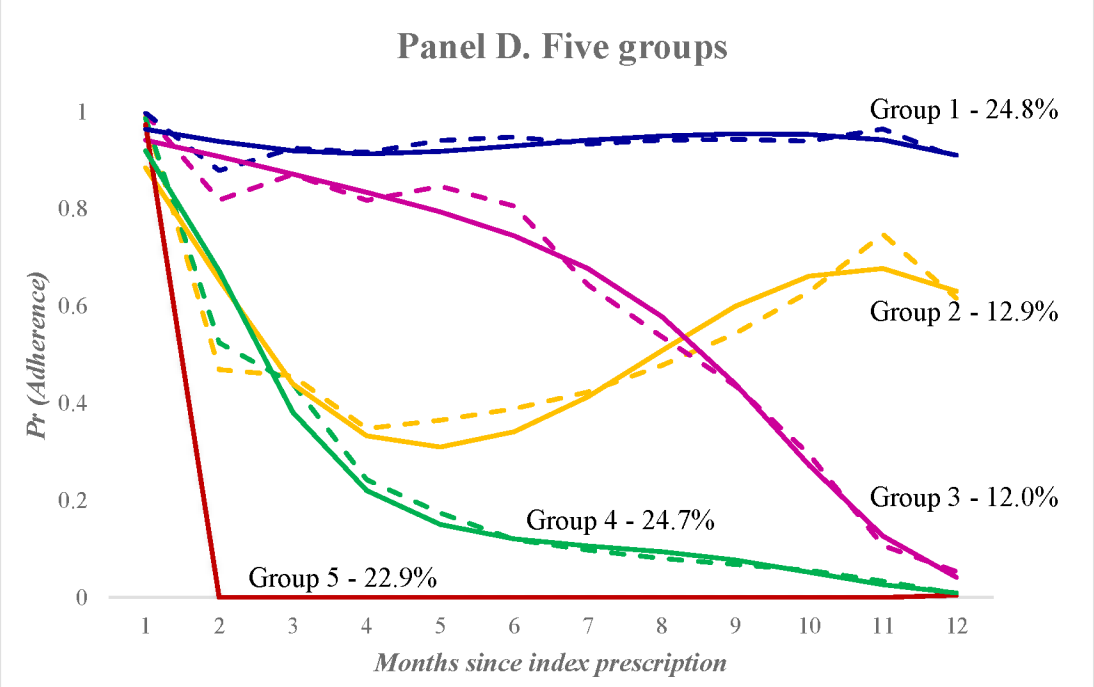


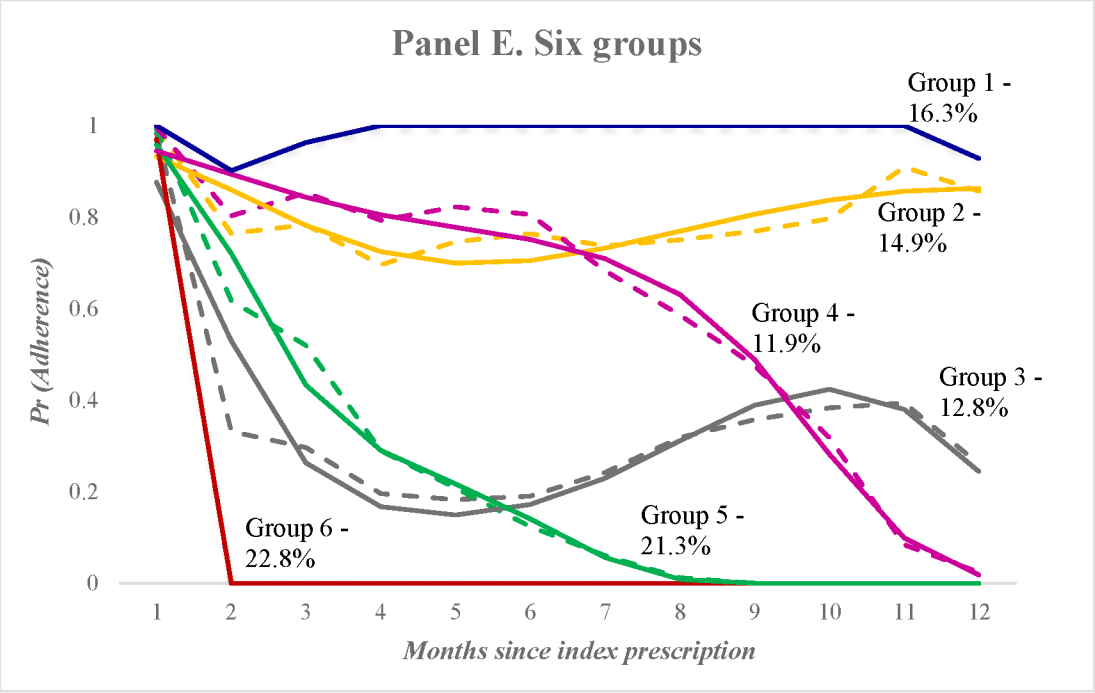
Figure 2. Medication adherence trajectories using 2 to 6 groups showing both predicted and observed trajectories (n=77297)






Panel C. Four groups
Pr(Adherence)
1
0.8
0.6
0.4
0.2
0
Group 1 - 27.9%
Group 2 - 16.7%
Group 3 - 16.2%
Group 4 - 39.2%
1 2 3 4 5 6 7 8 9 10 11 12
Months since index prescription


Panel D. Five groups
Pr (Adherence)
1
0.8
0.6
0.4
0.2
0
Group 1 - 24.8%
Group 2 - 12.9%
Group 3 - 12.0%
Group 4 - 24.7%
Group 5 - 22.9%
1 2 3 4 5 6 7 8 9 10 11 12
Months since index prescription



Dashed lines represent observed values and solid lines represent estimated values. The values alongside each line i.e. Group number with percentage, represent the proportion of the total population in that particular group

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ACADEMIC QUALIFICATIONS

Johns Hopkins Bloomberg School of Public Health, Baltimore *May 2016 (Expected)*

- Master of Science (ScM), Department of Epidemiology – Cumulative GPA: 4.0 (present)
- Thesis topic: Characterizing medication adherence to an oral glucose lowering drug, metformin, using group based trajectory models (Dr. Caleb Alexander)

B J Medical College, Ahmedabad, India *May 2008 - May 2011*

- Doctor of Medicine (MD) in Pharmacology
- Dissertation topic: Pharmacological Management of Pediatric Respiratory Tract Infections (Dr. Dikshit)

B J Medical College, Ahmedabad, India *Sept 2002 - March 2008*

- Bachelor of Medicine, Bachelor of Surgery (MBBS) – Cumulative GPA: 3.96

EXPERIENCE

Johns Hopkins Bloomberg School of Public Health **Baltimore, MD**

Research Assistant, Center for Drug Safety and Effectiveness *April 2015 - present*

- Primary analyst for systematic review of cardiovascular risks with exogenous testosterone therapy (Alexander)
- Primary analyst for an umbrella review of systematic reviews evaluating cardiovascular risk with exogenous testosterone therapy (Alexander)

Research Assistant, Department of Epidemiology *Feb 2015 - present*

- Assisting in a FDA sponsored project evaluating the utilization of generic drugs, factors influencing their prescription and dispensing, and patient relevant concerns about generics (Segal & Singh)
- Outlined the research protocol for one aim regarding identification of patient relevant concerns about generic drugs using FDA Adverse Events Reporting (FAERS) database (Singh)
- Developed algorithm to identify generic drugs in the FAERS database; validation ongoing
- Classified patient relevant concerns with generic drugs according to the NIH PROMIS framework

Research Analyst, Department of Epidemiology *Feb 2015 - Aug 2015*

- Drafted guidelines for antibiotic treatment of common infectious diseases including pneumonia, *Clostridium difficile* and urinary tract infections among residents of nursing homes for an externally funded project

Teaching Assistant, Department of Epidemiology *Sept 2015 – Oct 2015*

- Course title: Epidemiologic Methods I
- Conducted laboratory sessions in conjunction with instructors, communicated with students, piloted and graded tests

Teaching Assistant, Department of Epidemiology *Mar 2016 – May 2016*

- Course title: Methodologic Challenges in Epidemiologic Research
- Conducted laboratory sessions in conjunction with instructors, piloted and graded tests, aided students in developing research questions and addressing specific methodological challenges such as missing data, confounding bias, selection bias for a practicum project.

B J Medical College & GCS Medical College **Ahmedabad, India**

Assistant Professor, B J Medical College *May 2012 – May 2014*

- Trained second year medical students in Pharmacology in integrating their clinical knowledge with pharmacology and highlighting treatment of diseases of high prevalence in India
- Mentored post graduate students in Pharmacology and assisted them with their dissertation
- Organized the training of post graduate students in Pharmacology in form of seminars and journal clubs

Assistant Professor, GCS Medical College *Dec 2011 – April 2012*

- Established a Pharmacovigilance Unit in the hospital with promotion of reporting suspected adverse events among the clinicians and paramedical staff.
- Structured the training and manual of practical pharmacology to be used by second year medical students

Tutor/Postgraduate Resident, B J Medical College *May 2008 – Nov 2011*

- Pharmacology training of undergraduate medical, dental and nursing students
- Assisted in the revision of the manual "A Journal of Practical Pharmacology", introducing new clinical scenarios and clinical pharmacology exercises.
- Structuring of MCQs as an assessment tool for undergraduate medical students

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ADDITIONAL ACADEMIC ACTIVITIES

- Member of the Editorial Board of the *Indian Journal of Pharmacology* (Official Publication of the Indian Pharmacological Society) as an Editorial Assistant from 2010 to 2012.
- Member of the Editorial Board of the *Indian Journal of Pharmacology* (Official Publication of the Indian Pharmacological Society) as an Assistant Editor from 2013 onwards.

Professional Memberships

June 2015 – present	International Society of Pharmacoepidemiology (ISPE)
2009 – Present	Indian Pharmacological Society

Leadership

September 2015 – present	Co – president of the International Society of Pharmacoepidemiology - Student Chapter at Johns Hopkins Bloomberg School of Public Health 2015 – 2016 academic year

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PRESENTATIONS

1. Marimuthu SP, **Iyer G**, Segal JB, Singh S. Patient relevant outcomes associated with generic drugs in FDA's Adverse Event Reporting System. Abstract submitted for consideration – 32nd International Conference on Pharmacoepidemiology and Therapeutic Risk Management, August 2016.
2. Onasanya O, **Iyer G**, Lucas E, Singh S, Alexander GC. Association between Exogenous Testosterone and Cardiovascular Events: An Overview of Systematic Reviews. Abstract submitted for consideration – 21st Annual International Meeting of International Society for Pharmacoeconomics and Outcomes Research, May 2016.
3. Alexander GC, **Iyer G**, Lucas E, Lin D, Singh S. Cardiovascular Risks of Exogenous Testosterone Use among Men: A Systematic Review and Meta-Analysis. Abstract submitted for consideration – 21st Annual International Meeting of International Society for Pharmacoeconomics and Outcomes Research, May 2016.
4. **Iyer G**, Marimuthu SP, Segal JB, Singh S. Identification of Generic Drugs in the FDA Adverse Event Reporting System. Abstract accepted - ISPE Mid Annual Meeting, April 2016.
5. Alexander GC, **Iyer G**, Lucas E, Lin D, Singh S. Cardiovascular Risks of Exogenous Testosterone Use among Men: A Systematic Review and Meta-Analysis. Poster presentation at 'Centennial Poster Session – Future Studies' organized by Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore on November 3rd, 2015.

SCIENTIFIC PUBLICATIONS

Peer reviewed Journal Articles

1. Desai CK, **Iyer G**, Panchal JP, Shah SP, Dikshit RK. An Evaluation of Knowledge, Attitude and Practice of Adverse Drug Reaction Reporting among Prescribers at a Tertiary Care Hospital. Perspectives in Clinical Research. 2011;2:129-36.

2. Desai MK, **Iyer G**, Dikshit RK. Antiretroviral Drugs: Critical Issues and Recent Advances. Indian Journal of Pharmacology. 2012;44:288-98.

3. **Iyer G**, Patel PP, Panchal JP, Dikshit RK. An Analysis of the Pharmacological Management of Respiratory Tract Infections in Pediatric In-Patients at a Tertiary Care Teaching Hospital. International Journal of Medicine and Public Health. 2013;3:140-5.

4. **Iyer G,** Alexander GC. Cardiovascular risk associated with Clarithromycin. British Medical Journal. 2016;352:i23.

5. Alexander GC, **Iyer G,** Lucas E, Lin D, Singh S. Cardiovascular Risks of Exogenous Testosterone Use among Men: A Systematic Review and Meta-Analysis. Under review.

6. Onasanya O, **Iyer G,** Lucas E, Singh S, Alexander GC. Association between Testosterone and Cardiovascular Risks: A Review of Systematic Reviews. Under review.

7. Desai MK, Panchal JP, Shah SP, **Iyer G.** Evaluation of Impact of Teaching Clinical Pharmacology and Rational Therapeutics to Medical Undergraduates and Interns. Under review.

8. Lee C, **Iyer G,** Liu Y, Bamba N, Ligon C, Mathioudakis N. The Effect of Vitamin D Supplementation on Glucose Homeostasis in Type 2 Diabetes Mellitus: A Systematic Review and Meta-analysis of Intervention Studies. Under development.

Book chapters

1. Standard Treatment Guidelines: A Manual for Medical Therapeutics. Eds: Desai MK, Shah SP, **Iyer G**. Gujarat Medical Services Corporation Limited, 2014.

2. Rowe T, **Iyer G.** Challenges to Diagnosis and Management of Infections in Older Adult. In "New Directions in Geriatric Medicine: Concepts, Trends, and Evidence Based Practice." Ed: Lindquist LA. Springer Nature Publications, 2015. In press.

Articles not peer reviewed

1. **Iyer G**, Alexander GC. Re: Cardiovascular outcomes associated with use of clarithromycin: population based study. BMJ. 2016;352: h6926.